Is the Testis a Chemo-Privileged Site? Is There a Blood–Testis Barrier?

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The incidence of testicular cancer, primarily seminoma, has been increasing in many countries, including the United States. The testis is often the site of residual cancer after adequate treatment with systemic chemotherapy. The blood-testis barrier is commonly cited as the explanation for residual tumor within the gonad after chemotherapy and as the indication for delayed orchiectomy. Conversely, complete eradication of viable tumor from the primary site is common and argues against the testis as a "tumor sanctuary." Residual tumor is also demonstrated within metastatic foci, and the disparity between the histopathologic response of the primary tumor and metastatic sites may be best explained by tumor heterogeneity and multiple tumor clones. Regardless of the scientific and academic arguments, delayed radical orchiectomy remains an important part of treatment for patients undergoing primary chemotherapy.
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Key words: Testicular cancer • Blood–testis barrier • Orchiectomy • Chemotherapy

New cases of testicular cancer and deaths from the disease were estimated at 8250 and 370, respectively, for 2006 in the United States.[1] Although the reason is unknown, the incidence of testicular cancer, primarily seminoma, has been increasing in many countries, including the United States. Advances in surgical technique, radiation therapy, and chemotherapy for testicular cancer have resulted in a steady rise in the expected 5-year survival rate, which now exceeds 95%.[1] Despite this encouraging trend, the surgical treatment of patients with

testicular masses continues to be examined and refined.

Radical orchiectomy, performed through an inguinal incision with high ligation of the spermatic cord, is traditionally accepted as the first step in diagnosis and treatment of patients with testicular neoplasms. Extirpation of the affected testicle is curative for the vast majority of patients with localized disease. In addition, the specimen provides histologic diagnosis and pathologic information useful for determining the risk of lymphatic spread of the cancer, with minimal morbidity.

In the setting of presumed extragonadal germ cell tumors and advanced germ cell cancers with life-threatening metastatic disease, chemotherapy may be initiated before orchiectomy. In these select patients, a diagnosis of germ cell neoplasm is made on the basis of biopsy of an extragonadal site or on the basis of elevated tumor markers. Delayed orchiectomy is recommended to confirm complete response of the primary tumor to systemic chemotherapy.[2] The necessity of such a delayed orchiectomy procedure calls into question whether the testicle is truly a sanctuary site, protected from exposure to systemic chemotherapy. In this article, we present the case of a patient with metastatic testicular cancer, which initiated our debate regarding whether there is a blood–testis barrier (BTB) and its clinical relevance to the treatment of testicular carcinoma.

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Case Report

A 36-year-old African American man presented with a 2-month history of a rapidly enlarging, painless scrotal mass, 10-lb unintentional weight loss, fatigue, malaise, and anorexia. Physical examination confirmed the presence of a large, firm, nontender left scrotal mass, left flank mass, and a left supraclavicular mass. Laboratory studies revealed an elevated serum creatinine level of 2.0 mg/dL and anemia, with a hematocrit of 31.5%. Tumor marker analysis demonstrated normal alpha-fetoprotein levels but elevated levels of human chorionic gonadotropin (HCG) and lactate dehydrogenase, 324 and 1029 U/L, respectively. Ultrasonography of the scrotum identified a 9 × 6 × 5-cm heterogeneous intratesticular mass. Abdominal computed tomography (CT) demonstrated significant bilateral retroperitoneal lymphadenopathy, a large mass adjacent to the left renal hilum, and bilateral hydronephrosis. CT evaluation of the chest and neck confirmed the presence of a solid, 7-cm left supraclavicular mass.

The patient underwent retrograde placement of bilateral ureteral stents and had a subsequent modest lowering of the serum creatinine value, to 1.7 mg/dL. A renal scan then demonstrated persistent obstruction of the left kidney. A percutaneous nephrostomy tube was placed, with subsequent normalization of the patient's creatinine level. A percutaneous needle biopsy of the left supraclavicular mass was insufficient for diagnosis but was "suspicious for a neoplastic process." Unfortunately, the patient then refused further percutaneous or surgical procedures. With a presumptive diagnosis of advanced stage 3 testicular cancer of unknown histology, the patient was started on chemotherapy with bleomycin, etoposide, and cisplatin. After chemotherapy, the patient's tumor marker levels normalized. A persistent testicular mass was noted on physical examination, unchanged from initial presentation. The patient reluctantly agreed to a left radical orchiectomy. Final pathology revealed necrotic tumor with features suggestive of germ cell tumor, but no viable tumor was identified in the orchiectomy specimen.

Point (Dhiren S. Dave, MD): Evidence Supporting the Existence of the BTB

Several clinical observations suggest the existence of the BTB. Principally, spermatogenesis, beginning at puberty, involves the expression of novel cell-surface antigens after the immune system has refined the ability to distinguish self from non-self. Sperm located within the testis, however, do not elicit an immune response. Additionally, whereas macrophages and lymphocytes are commonly found within the interstitial spaces of the testis, these antigen-presenting cells are rarely seen within the seminiferous tubules. These observations have led to the concept of the testicle as an immune-privileged site.

Further evidence of the existence of the BTB evolves from the treatment of childhood leukemias, in which the highest rates of relapse occur within the central nervous system (CNS) and testes, both believed to be protected from exposure to systemic chemotherapy, presumably as a result of the blood–brain barrier and BTB, respectively. Consequently, gender remains an important prognostic factor in treatment of acute lymphoblastic leukemia, with testicular relapses reported in up to 17% of patients after complete remission.[3-5] These rates are comparable to the rate of relapse within the CNS in this same group of patients.[6,7] Additional clinical

evidence comes from retrospective studies of men with primary testicular lymphomas treated with chemotherapy. Essentially all treatment failures involve either the CNS or the contralateral testis, with a 40% to 45% rate of testicular relapse in some series.[8]

Furthermore, chemotherapeutic agents achieve reduced concentrations within the interstitium of the testis when compared with plasma levels, suggesting that a certain "barrier" property exists between capillaries and the interstitial space.[9,10] Multiple studies have demonstrated the inability of specific large and small molecules to cross between the testicular interstitial space and germinal tubules.[11-13]

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The Anatomy of the BTB

The testis consists of approximately 250 lobules, each composed of 1 to 4 seminiferous tubules. The space between these tubules, known as the *interstitial space*, harbors testosterone-producing Leydig cells and numerous capillaries. Within the lobules, ultrastructural studies in rats have shown that the Sertoli cells are connected to one another along the basolateral aspect by tight junctions, which form a physical barrier against the migration of large molecules into the tubular environment.[11,14-16] Tight junctions have also been demonstrated between capillary endothelial cells, suggesting that endothelial tight junctions also contribute to the mechanical BTB.[11,17] Tight junctions have also been identified between myoid cells and are thought to contribute another layer of protection for developing sperm.[11]

In addition to the mechanical barrier provided by tight junctions, an active system of transmembrane transporters is postulated to remove small lipophilic molecules from the intertubular space. P-glycoprotein and multidrug resistance–associated protein 1 (MRP1) are 2 examples of transmembrane adenosine triphosphate–dependent efflux pumps thought to decrease the concentration of cytotoxic compounds within the testis. Interestingly, these proteins were first identified as part of a group of proteins conferring resistance to chemotherapy by various tumors.[18,19] P-glycoprotein is heavily expressed at the basolateral side of capillary endothelial cells, as well as at the myoid cell layer,[20] and is known to excrete a number of different compounds, including carcinogens, hormones, and bilirubin, from the intratubular compartment.[21,22] Animal models have confirmed that animals lacking P-glycoprotein show increased tubular concentrations of cytotoxic agents, such as vincristine, supporting the concept of the efflux pump barrier.[23] Studies in rats have shown that MRP1 is expressed on the basal surface of Sertoli cells, as well as on Leydig cells, protecting these cells from cytotoxic compounds by pumping them into the interstitial space.[24]

The BTB in Germ Cell Cancers

Although the presence of a BTB can be inferred from the previously mentioned clinical experience and from laboratory studies, the need to perform a radical orchiectomy after treatment with chemotherapy, especially when no evidence of residual disease exists, has been questioned for many years. Multiple retrospective series have examined delayed orchiectomy after treatment with systemic chemotherapy for advanced germ cell tumors.[25-31] Table 1 summarizes the rates of residual viable tumor within the testis after systemic chemotherapy. Persistent viable primary tumor was found in 8.3% to 37.5% of patients, and several of these studies have demonstrated the presence of residual viable tumor in the testis despite successful eradication of metastatic disease.[25,27,31] This argues that a BTB interferes with the ability of systemic chemotherapy to successfully treat germ cell cancers within the testis.

Counterpoint (John T. Leppert, MD): The BTB Is Not Clinically Significant

At first review, the data presented above by Dr. Dave strongly argue in favor of a clinically significant BTB. However, careful examination of published reports of delayed orchiectomy after systemic chemotherapy calls into question whether the BTB is relevant to the treatment of germ cell cancers.

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In the largest published series, Leibovitch and colleagues[29] reviewed

Table 1
Pathology of Orchiectomy Specimen After Treatment With Systemic Chemotherapy for Metastatic Testicular Cancer

	N	Fibrosis/Scar (%)	Teratoma (%)	Viable Tumor (%)
Leibovitch I et al[29]	160	43.7	50	25
Ondrus D et al[30]	36	50	41.7	8.3
Simmonds PD et al[2]	24	62.5	25	12.5
Chong C et al[26]	16	N/A	N/A	25
Snow BW et al[31]	8	N/A	N/A	37.5
Greist A et al[28]	20	55	30	15

NA, not applicable.

160 patients with nonseminomatous germ cell carcinoma who underwent delayed orchiectomy after chemotherapy. Pathologic evaluation of the testicle identified necrotic tumor and scar in 70 patients (43%) and pure teratoma in 50 (31.2%), whereas 40 patients (25%) demonstrated persistent viable tumor. The systemic response to chemotherapy in these 40 patients was also evaluated by concurrent retroperitoneal lymph node dissection. Seventeen (42%) of these 40 patients demonstrated sterilization of the retroperitoneum by systemic chemotherapy, whereas 16 patients (40%) harbored teratoma and 7 (18%) were found to have residual viable tumor. The histopathologic findings in the postchemotherapy testis and retroperitoneal lymph node specimens correlated in only half of the cases. Indeed, of the 70 patients with complete eradication of the testicular tumor burden, 35 harbored residual retroperitoneal disease. Furthermore, the pathologic findings within the testicle specimen did not correlate with the clinical relapse rate or the cancer-specific survival.

Other investigators have published similar results. Snow and coworkers[31] found residual germ cell cancer in the delayed orchiectomy specimens of 3 of 7 patients after treatment with chemotherapy. The remaining 4 specimens showed either testicular atrophy or pathologic evidence of tumor necrosis. Of note, 2 of the 3 patients with residual testicular tumor burden progressed to have distant disease relapse and required further systemic treatment. Chong and colleagues[26] also reported similar results. The investigators studied 16 patients with metastatic disease who underwent initial chemotherapy followed by delayed orchiectomy for unrecognized primary tumor (3 patients) and for life-threatening distant metastatic disease (13 patients). They found that 3 of 13 patients (23%) with apparent complete response after chemotherapy and 1 of 3 (33%) with partial response harbored residual viable tumor within the testicle.

Although the BTB may indeed be a clinically and anatomically significant entity, it may not completely account for the discrepancy in response to chemotherapy between the primary and metastatic sites in the context of therapy for testicular cancer. Nonseminomatous germ cell cancers often present with multiple cell lines within a single tumor. This multiclonal phenomenon may provide additional explanation for the varied clinical response of germ cell tumors within the testicle, as well as in extragonadal locations. This tumor heterogeneity may be a result of spontaneous mutations, selective clonal metastasis, or differentiation of multipotential tumor cells along different lines.[26,32,33] As such, an argument can be made to remove the testicle that harbors the primary tumor to ensure successful treatment and eradication of the particular clonal variants, which may not respond to systemic treatment. This line of reasoning is in contrast to the traditional paradigm that orchiectomy should be performed because the BTB prevents adequate delivery of chemotherapy to the primary site.

Conclusions

The available data show that the testis is often the site of residual cancer after adequate treatment with systemic chemotherapy. The BTB is commonly cited as the explanation for residual tumor within the gonad after chemotherapy and as the indication for delayed orchiectomy. Conversely, complete eradication of viable tumor from the primary site is common, as demonstrated by the included case report, and argues against the testis as a "tumor sanctuary." Residual tumor is also demonstrated within metastatic foci, and the disparity between the histopathologic response of the primary tumor and metastatic sites may be best explained by tumor heterogeneity and multiple tumor clones. Regardless of the scientific and academic arguments, delayed radical orchiectomy remains an important part of treatment for patients undergoing primary chemotherapy. This procedure, performed alone or at the time of retroperitoneal lymph node dissection, is safe and is associated with minimal morbidity. Additionally, delayed orchiectomy provides important

postchemotherapy staging information, clinical information that may affect adjuvant treatment strategies and the potential for resection of occult residual disease. ■

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Main Points

- Several clinical observations suggest the existence of the blood–testis barrier (BTB).
- Evidence from retrospective series argues that a BTB interferes with the ability of systemic chemotherapy to successfully treat germ cell cancers within the testis.
- Conversely, it can be argued that although the BTB may be a clinically and anatomically significant entity, it may not completely account for the discrepancy in response to chemotherapy between the primary and metastatic sites in the context of therapy for testicular cancer.
- Regardless of the scientific and academic arguments, delayed radical orchiectomy remains an important part of treatment for patients undergoing primary chemotherapy.